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THREAT-SPECIFIC BIASES IN FXS

Children with Fragile X Syndrome Display Threat-Specific Biases Toward Emotion

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Abstract

Background: Fragile X syndrome (FXS) is the most common form of inherited intellectual disability. FXS is caused by a silencing of the \textit{FMR1} gene that results in a loss or absence of the gene’s protein product, fragile X mental retardation protein. The phenotype of FXS is consistently associated with heightened anxiety, though no previous study has investigated attentional bias towards threat, a hallmark of anxiety disorders, in individuals with FXS.

Methods: The current study employs a passive viewing eye tracking version of the dot probe task to investigate attentional biases towards emotional faces in young children with (N=47) and without FXS (N=94).

Results: We found that the FXS group showed a significantly greater bias towards threatening than positive emotions. This threat specificity was not seen in either a mental age matched or chronologically age matched group of typically developing (TD) children. Unlike the TD groups, the FXS group showed no bias towards positive emotion.

Conclusions: The current study shows that children with FXS have a significant bias towards threatening information, an attentional profile that has been linked with anxiety. It also supports utilization of eye tracking methodology to index neural and attentional responses in young children with FXS.
Children with Fragile X Syndrome Display Threat-Specific Biases Toward Emotion

Fragile X syndrome (FXS) is an X linked disorder caused by a trinucleotide repeat expansion on the \textit{FMR1} gene on the X chromosome. The full mutation of the disorder occurs when this CGG repeat expansion number is greater than 200, which causes a loss of function of the gene via methylation (1). When fully methylated, the gene is silenced and no longer produces its protein product Fragile X Mental Retardation Protein (FMRP), which is crucial for proper synaptic functioning (2,3). The full mutation, FXS, occurs in approximately 1 in 2,500-4,000 males and 1 in 7,000-8,000 females (4).

The phenotype of FXS includes intellectual disability, attention problems, and anxiety (5). Cordiero et al. (2010) reported that upwards of 82.5% of individuals with FXS, ages 5-35 years had clinical levels of anxiety. Social phobia and specific phobia were the most common, with 58% of the sample qualifying for multiple anxiety disorder diagnoses (6). Social phobia and PTSD are more common in adults than children with FXS (6). Talisa et al. (2014) showed that young children with FXS who present without anxiety disorders show less attention problems, hyperactivity, and aggression than those with heightened anxiety or those with heightened anxiety and ASD (7). Rogers et al. (2001) also theorizes that social anxiety presenting early in development of individuals with FXS may lead to shyness and problems with social interactions (8).

\textbf{Emotion and the Brain in FXS}
Olmos-Serrano and Corbin (2010) provided a review of the importance of amygdala and frontal dysfunction in FXS that focuses on adults, but stresses the need for developmental work (9). This amygdala-prefrontal circuit is crucial in non-syndromic anxiety, and in FXS (10). Individuals with anxiety atypically deploy attention to threatening stimuli more than control individuals and interpret ambiguous information as threatening. These findings have been documented in children with anxiety as early as school-age (11). Holsen et al. (2008) also linked impairments in hippocampal activity during emotional face processing as a precursor to social anxiety, specifically for individuals with FXS (12).

Kim et al. (2012) showed that the amygdala is functionally atypical in adolescents on the FX spectrum (13). The fMRI study showed that amygdala activation failed to increase more to fearful than happy faces, as was observed in the control participants. Importantly, the individuals who presented the greatest anxiety levels were those whose neural signature to threat was the most atypical. This study supports a threat-specific processing profile in FXS that is linked to anxiety and related to, or potentially caused by, atypical functioning of the amygdala. Further exploration of these processes and their developmental origins in younger populations of children with FXS is unfeasible given the behavioral and attentional requirements of the MRI environment. The present study presents an alternative methodology that is appropriate for use in young and intellectually disabled populations that can describe the cognitive phenotype of affective processing in young children with FXS.

**Threat Bias in Anxiety Disorders**
One promising avenue of exploration is attentional bias patterns to affect in young children with FXS. While, due to methodological and measurement limitations, we cannot directly measure anxiety in infants with FXS, we can use attentional patterns towards affect, specifically threat, to investigate the phenotype of FXS, which can help elucidate the underlying cognitive mechanisms related to heightened anxiety in FXS.

Bar-Haim and colleagues (2007) reported that non-anxious, typically developing adults did not show attentional biases towards threat, and that a significant threat bias exists in individuals with nonsyndromic clinical and subclinical anxiety (14). Anxious children and adults showed similar patterns, though effect sizes are often smaller and variability is often greater in younger populations. Mogg et al. (2007) showed that bias patterns may differ based on the age of the individuals and on the timing parameters being used (15). It has also been reported that adolescents with anxiety show attentional biases specifically to threat regardless of specific diagnosis (16). These findings provide support for the theory that there may be a basic “error” in information processing in anxiety, and they provide a framework for understanding anxiety and its mechanisms in young children with FXS by implicating attentional behavior towards threatening information in the environment as an important marker of this information processing error.

The Dot Probe Task

Attentional bias towards threat has typically been measured using the dot probe task (DPT). The classic version of the DPT consists of a brief presentation of two faces, usually paired by emotion: neutral-neutral, happy-neutral, and angry-neutral (17). These faces are followed by a probe that appears on the same side of one of the faces before it.
On trials that are congruent, the probe appears on the same side of the screen as the emotional face. In incongruent trials the probe follows on the same side as the presentation of the neutral face. Individuals are tasked to indicate (usually with a button press) which side of the screen the probe appears on. The theory behind the task is people will be able to respond faster to a stimulus that appears in an attended region of their visual field than to a stimulus that appears in an unattended region (18). Attentional biases are calculated using the reaction time to the probe on incongruent versus congruent trials. If individuals are faster at detecting probes that appear in the same spatial location as the emotional faces it indicates their attentional system was biased towards that stimulus.

Children as young as 5 years old have been administered the classic DPT (19), but the cognitive impairments that are present in early childhood in FXS make it challenging to administer the task. Likewise, infants lack the motor control and cognitive abilities to follow instructions and provide a motor response on the traditional DPT. Thus, the modification of the DPT to a completely passive-viewing eye tracking paradigm, as we have done in the present study, allows for reliable measurement of attention to affect, a variable highly related to anxiety, in infants and to all individuals with FXS, regardless of age. This utilization of eye tracking to index attentional biases towards threat is a prime example of how eye tracking can be used to understand early cognitive and underlying neural processes in this atypically developing population.

The Current Study

FXS is an excellent candidate disorder for investigating the underlying cognitive mechanisms behind anxiety, and these cognitive mechanisms are an ideal target for
investigation early in development. We currently do not have reliable and empirically validated measures of anxiety for very young individuals, and attentional biases towards threat in FXS, as measured by the DPT, have never been investigated. Given the correlation between anxiety and attentional biases towards threat, and the high percentage of anxiety symptoms in FXS, these biases may constitute a biomarker for anxiety in FXS, and can aid in exploring the clinical phenotype of FXS.

We aimed to explore attentional bias patterns toward affect in young children with FXS. This could be the first step to developing an effective, sensitive and empirically objective metric of anxiety risk in young individuals with FXS. We investigated attentional biases to emotion in young children with FXS using a modified, passive-viewing eye tracking version of the DPT using angry and happy faces. To control for cognitive level and overall development, we collected data on mentally age-matched (MA) and chronologically age-matched (CA) samples of typically developing (TD) children. The current study initially investigated any preliminary relations between attentional bias patterns and gender, given the large phenotypic differences seen between males and females with FXS. It then explored any relation with ASD symptomology, given the high comorbidity of ASD in FXS. Then we aimed to validate use of this modified version of the DPT in FXS. Given previous research on atypical neural processing (specifically of negative affect) in FXS, we predicted that the FXS group would show a significant attentional bias on trials that included threatening faces and not on trials that included happy faces.

Methods and Materials

Participants
A total of 47 children with FXS (8 females) were evaluated at the UC Davis MIND Institute. The children’s chronological ages ranged from seven months, 29 days to 68 months, 2 days ($M=39$ months 28 days, $SD=17$ months 23 days). Cognitive level was assessed in the FXS group using the Mullen Scales of Early Learning (20), a standardized developmental assessment used for children age 3-60 months. It consists of five subscales: gross motor, fine motor, receptive language, expressive language, and visual reception. The mental age of each participant in the FXS group was calculated by averaging the age equivalencies across four domains (excluding gross motor) and converting that to months and days. We excluded gross motor from this calculation, as the scores are less valid in children above the age of 33 months (20). The FXS sample’s mental ages ranged from 5 months, 15 days to 51 months, 21 days ($M=21$ months, 29 days, $SD=11$ months, 3 days).

Autism symptomology was measured in a subset of the children with FXS (28 out of 47) who were administered either an ADOS module 1 or 2, depending on their cognitive ability, by a trained clinician (21). Of the 28 children with FXS who completed an ADOS, 18 met criterion for ASD (64%).

While all FXS participants had a clinically-confirmed diagnosis in their medical record, FXS allele status was confirmed by $FMR1$ DNA testing for a subset of the participants who consented to a blood draw during their research visit (thirty-five of the forty-seven). This subset sample consisted of 20 individuals with the full mutation (five females), eight with methylation mosaicism (one female), and seven males with size mosaicism. No individuals with the premutation of the disorder were included. All statistical analyses reported below were completed with and without the 12 individuals
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who didn’t have confirmatory DNA testing, and no differences were seen; therefore, results for the entire FXS sample are reported herein.

Two discrete TD comparison samples were recruited through letters to families in surrounding areas around Davis, California and were given a certificate and a book for participating. The first sample were matched to the MA of each individual in the FXS sample and the two groups’ mental ages were not statistically different ($t(47)=.013 \ p=.99$). The MA-matched group had 47 participants (8 females) with chronological ages (which in a TD sample should reflect the mental age of the child) ranging from 5 months, 14 days to 51 months, 11 days ($M=21 \text{ months} 28 \text{ days}, \ SD=10 \text{ months} 29 \text{ days}$). The second sample of TD children were matched to the CA of each individual in the FXS sample and the two groups’ chronological ages were not statistically different from one another ($t(92)=.10 \ p=.92$). The CA matched group had 47 participants (8 females) with CA ranging from 8 months, 9 days to 67 months, 22 days ($M=40 \text{ months} 9 \text{ days}, \ SD=18 \text{ months} 1 \text{ day}$). None of the control participants were tested for developmental disabilities. A breakdown of ages across the three groups can be seen in Table 1. The Institutional Review Board of UC Davis approved the experimental protocol, and informed consent was obtained from a parent or caregiver of each participant.

Stimuli

The task was presented in two blocks, each consisting of 40 trials (see Figure 1 for task details). The task began with a 1000ms central fixation cross, followed by a 500ms face pairing that was followed immediately by a 1500ms asterisk probe that appeared in the same spatial location as one of the previous faces (see Figure 1). There were three categories of face pairings: thirty-one angry paired with neutral, thirty-two
happy paired with neutral, and seventeen neutral paired with neutral. Expressions were modeled by twenty-eight different actors from the NimStim stimulus set (22). The angry, happy, and neutral closed-mouth images of fourteen male and fourteen female Caucasian, African American and Asian faces were used. Images were trimmed so that all hair was removed from the image. Identity, sex and race of the face, emotion, probe side, and trial congruency were all randomized.

**Apparatus**

Stimuli were presented on a 17-inch Tobii 1750 LCD binocular eye tracker (1280 x 1024 pixels resolution) to record fixations during the task. Children were seated on average 60cm away from the eye tracker on a parent’s lap. Eye tracking data were collected at a sample rate of 50 Hz. The average accuracy of the recorded eye coordinates was about 0.5°, which is approximately 0.5 cm at a viewing distance of 60 cm. The average accuracy in timing is 25-35ms. Drifts are compensated with an average error of 0.5°. When one eye could not be measured, data from the other eye were used to determine the gaze coordinates. The recovery time to full tracking ability after an offset was about 100ms. Fixations were defined using the Tobii fixation filter, such that maximum angle between fixations was 0.5° and fixations had to be longer than 60ms. To control the presentation timing of the task, video stimuli of all trials were created using iMovie and were displayed using Tobii Studio. A standard five-point Tobii calibration was administered for all participants. Recalibration occurred if any single point was missed. Our goal was to only begin the task once all 5 points had a successful calibration; however, the minimum requirement to proceed with the task was a successful calibration of the center point for each eye.
Data analysis

A trial was included if the participant fixated the area of interest (AOI) around the probe during the 1500ms probe presentation time. The AOI was defined as a circle around the probe with a .5-inch diameter. A bias score was calculated for each participant by subtracting the average latency to fixate the asterisk probe on congruent trials from incongruent trials. A positive value represented a vigilance for or bias towards the emotional face, a score around zero indicated no bias and a negative score indicated an avoidance of the emotional face.

First, given the genetic and phenotypic differences between genders in FXS, exploratory analyses investigated any possible gender effects across the three groups on bias scores, and given the high comorbidity of ASD in FXS, we also probed any impact that autism symptom severity had on the key variables in the study. We then investigated the feasibility of administering the task in the FXS population by statistically comparing the overall latency and number of trials for each group. We then compared the magnitude of attentional biases on both angry and happy trials within group using a repeated measures ANOVA to investigate if the attentional bias patterns in the FXS group differ from those of the two TD groups, and to compare each group’s bias scores with chance levels in both emotional conditions to investigate the magnitude of affective bias scores within group.

Results

One way ANOVAs for each emotion by gender revealed that happy bias and angry bias values did not significantly differ by gender in any of the three groups (all $F$’s $<1$, $p$’s $.05$). Autism severity, as measured by the ADOS in a subset of children with
FXS, did not correlate with number of trials completed ($r=.26$, $p=.18$), overall latency ($r=.07$, $p=.72$) or either happy ($r=-.31$, $p=.11$) or angry bias scores ($r=-.01$, $p=.96$).

To measure feasibility of administration of the task, we compared numbers of trials on which children provided latencies to the probe across groups. Children with FX provided on average 62.21 trials out of 80, or 78% of the task. Children in the MA and CA groups provided latencies to the probe on an average of 70.68 trials (88%) and 71.38 trials (89%), respectively. These values were significantly different from one another, $F(2,138)=10.73$, $p<.001$, with FXS being significantly lower than both the MA group ($t(92)=3.48$, $p<.001$) and the CA group ($t(92)=3.73$, $p<.001$), and the two TD groups not being different from one another ($t(92)=.433$, $p=.66$). The details related to these measures are presented in Table 1.

The latency values of individuals with FXS were on average slower than the CA group, $t(92)=3.03$, $p<.01$, $d=.63$, but not significantly different from the MA group’s overall latencies $t(92)=.75$, $p=.46$, $d=.15$. Overall latency, regardless of trial type, was not significantly correlated with chronological age ($r(45)=-.08$, $p=.60$) or mental age ($r(45)=-.02$, $p=.87$) in the FXS group, but it was negatively correlated in both the MA, $r(45)=-.49$, $p<.00$, and the CA, $r(45)=-.56$, $p<.00$, TD groups, indicating that only the TD children are showing reduced latency with age. Overall latency was also not correlated with MA in the FXS group ($r=-.02$, $p=.89$).

Once measures of task efficacy were evaluated, the primary hypothesis of the study, to investigate the magnitude and emotional specificity of attentional biases toward affect across these three groups, was examined. Average bias scores (presented in Table 1) were entered into a repeated-measures ANOVA with one within-subjects factor:
emotive (angry or happy); and one between-subjects factor: group (FXS, CA, or MA).

The analysis showed no significant main effect of emotion, $F(1,138)=1.96$, $p=.16$, $\eta^2_p=.014$, or group, $F(1,138)=.002$, $p=.98$, $\eta^2_p<.00$, but did show a significant group by emotion interaction, $F(2,138)=3.29$, $p=.04$, $\eta^2_p=.04$. To explore this interaction, simple effects were investigated by performing a separate paired samples $t$-test on the bias score between emotions within each group. These tests revealed a significantly greater bias on angry trials than happy trials in the FXS group, $t(46)=2.57$, $p=.01$, $d=.54$, but not in the CA group, $t(46)=.33$, $p=.74$, $d=.07$, or the MA group, $t(46)=.16$, $p=.88$, $d=0.03$, indicating that children with FXS, but not CA- or MA-matched TD children, were significantly more biased toward emotion on angry trials than happy trials. Simple effects were also investigated by performing a separate paired samples $t$-test on the bias scores for each emotion between groups. While the angry bias scores in the FXS group were twice that of the TD groups’, they were not significantly greater than either the MA ($t(92)=1.51$, $p=.14$, $d=.31$) or CA ($t(46)=1.58$, $p=.12$, $d=.33$) groups’ scores. Similarly, while the FXS group’s bias scores to happy were closer to zero, they were not significantly less than either the MA ($t(46)=1.69$, $p=.09$, $d=.35$) or CA ($t(46)=1.71$, $p=.09$, $d=.35$) groups’ scores.

For angry bias scores, one-sample $t$-tests indicated that scores were significantly greater than a chance bias score of zero (zero indicating no difference in latency between the congruent and incongruent trials) for children in the FXS group ($M=81.62$, $SD=129.23$; $t(46)=4.33$, $p<.001$, $d=0.54$), the CA group ($M=40.53$, $SD=122.23$; $t(46)=2.27$, $p=.02$, $d=0.33$), and the MA group ($M=43.17$, $SD=118.09$; $t(46)=2.51$, $p=.02$, $d=0.36$). For happy bias scores, one-sample $t$-tests indicated that scores were significantly
greater than a chance level of zero for children in the CA group ($M=48.92$, $SD=102.18$; $t(46)=3.28$, $p=.002$, $d=0.44$), and the MA group ($M=46.52$, $SD=89.48$; $t(46)=3.56$, $p=.001$, $d=0.47$), but not for children in the FXS group ($M=9.50$, $SD=129.23$; $t(46)=.540$, $p=.59$, $d=0.07$). Bias scores for each group can be seen in Figure 2.

**Conclusions**

The current study investigates attentional biases towards affect in young children with FXS. We employed eye tracking methodology to modify the DPT for use in both clinical and pediatric populations to better understand and explore the cognitive phenotype and attentional behavior of young children with FXS.

Children in the FXS group completed less trials than children in either TD group. This indicates a lessening in attentional behavior that is most likely related to syndrome-specific attentional deficits (1). However, the FXS sample still completed a significant portion of the task trials (78%), indicating that although their attentional impairments do impact their performance, they can reliably complete this modified version of the DPT. The FXS group showed a slower visual reaction time than the CA-matched group. This could be related to cognitive and attentional deficits seen in the FXS group. The overall latency of the FXS group was not significantly different from the MA-matched group, providing support for the idea that cognition ability, rather than physical maturation, is related to changes in latency. The findings related to latency provide support for analyzing the task in the traditional way (i.e., using a difference score between the incongruent and congruent trials). These difference scores allow examination of the task without being influenced by a group level difference in overall latency. Thus,
another strength of the task is that it allows for standardization of the clinical group’s data
to allow comparable analysis on the same measure with the TD groups.

In the FXS group, we see a significantly larger bias towards angry paired with
neutral stimuli than towards happy paired with neutral stimuli. This result is supported by
the previous literature demonstrating atypical processing, at the behavioral and neural
level, of affect by individuals with FXS (11). By contrast, no differences were seen in
bias scores between angry and happy conditions in either of the TD groups.

Angry biases were greater than chance level in all three groups, suggesting that
having some attentional bias towards threatening information is normative in young
children. The average angry bias score in the FXS group was double that of the TD
groups, though the difference was not significant. Happy bias scores in both TD groups
were also significantly greater than chance, though the FXS group’s average bias score
on happy trials was not. While the FXS group’s happy bias scores were closer to zero,
they were not significantly less than either of the TD groups’ scores. These findings
indicate that individuals with FXS are not showing the typical bias towards positive
affect, but instead are showing a threat-specific bias pattern. The fact that the between
group comparisons did not reach significance is most likely due to the high amount of
variability in the scores, but this highlights the importance of within group differences
between affective conditions. It is not simply the magnitude of the affective biases in
FXS that differentiate this group from the typical comparison groups, but it is the threat
specificity that is shown in their bias score patterns. These findings fit with those of
Crawford et al. (2016) which showed that, on an eye tracking task, individuals with FXS
preferentially allocated attention to negative emotion (disgust) more than they did to a positive emotion (23).

These findings could inform future treatment efforts. Bar-Haim (2010) reviews attention bias modification (ABM) in which individuals with attentional biases towards threat are systematically attentionally trained towards positive stimuli (24). Waters et al. (2008) have shown that ABM can positively impact anxiety levels of pediatric populations with non-syndromic anxiety (25). Given that ABM can be similarly modified into a passive viewing task as the current study modified the DPT, this could be an ideal treatment approach in FXS.

Future studies should recruit more females with FXS to have greater statistical power to explore whether gender plays. It would also have been preferable to have autism symptomology and genetic variables in the entire sample (rather than the subset we had in the current study), though the data on the subsets of the FXS group showed no trend of either playing a role in the observed attentional bias. Future studies with older individuals with FXS should measure anxiety concurrently with attentional biases to directly link attentional biases toward affect to the heightened anxiety seen in the population.

The current study adds to the literature suggesting that there is a lack of typical bias towards positive affect and a threat specificity in the processing of affective information in young individuals with FXS. Aberrant processing of affective information in FXS could be directly related to the heightened levels of anxiety that are seen in FXS, and both could be related to the previously-reported aberrant functioning of the amygdala in individuals with FXS. Given that the amygdala and its related neural structures are initially activated by the emotional faces in the DPT, our eye tracking task can be used as
an index of neural difference between individuals with FXS and TD, age-matched controls. The constraints associated with typical functional neuroimaging techniques severely limit their use with young populations with developmental disorders. Thus, carefully designed eye tracking tasks like the modified DPT presented here, may allow researchers to index brain responses without requiring the young child to undergo a more challenging neuroimaging procedure.
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References


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Table/Figure Legends

Table 1. Number of trials and performance to emotion by group.

Note: Age is presented in month.days, number of trials is out of a total of 80 trials, bias scores represent average latency (in milliseconds) to incongruent trials minus average latency to congruent trials. Chronological age values act as mental age values for both TD groups.

Figure 1. Trial sequence of the dot probe task.

Figure 2. Average bias scores by group. Error bars represent standard error.
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Note: Age is presented in month.days, number of trials is out of a total of 80 trials, bias scores represent average latency (in milliseconds) to incongruent trials minus average latency to congruent trials. Chronological age values act as mental age values for both TD groups.
500 ms
Incongruent trial

1500 ms

500 ms

1500 ms

Congruent trial